Investigational New Drugs (2022) 40:1274–1281
https://doi.org/10.1007/s10637-022-01299-3

RESEARCH

Phase I study to evaluate of the gastric pH-dependent drug interaction between famitinib and the proton pump inhibitor omeprazole in healthy subjects

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Received: 10 August 2022 / Accepted: 28 August 2022 / Published online: 10 September 2022

Summary

To evaluate the potential gastric pH-dependent drug-drug interaction (DDI), safety and tolerability of famitinib co-administered with omeprazole in healthy subjects. Twenty healthy subjects were enrolled in a single-center, single-arm, open-label, fixed-sequence study. Famitinib was administered as a single oral 25 mg under a fasting condition on day 1, omeprazole (40 mg once daily) was given on days 10–14, concomitantly with famitinib on day 15, and for the follow-up 7 additional days (days 16–22). Blood samples were collected for the pharmacokinetic analysis of famitinib and its metabolite SHR116637 following each famitinib dose. Safety and tolerability were assessed during the whole progress via clinical laboratory tests. The least-squares geometric mean ratios (GMRs) (90% CI) of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ for famitinib combined with omeprazole to famitinib alone were 0.989 (0.953, 1.027), 0.956 (0.907, 1.007) and 0.953(0.905, 1.005) respectively. For the metabolite SHR116637, their GMRs (90% CI) of the above parameters were 0.851 (0.786, 0.920), 0.890 (0.838, 0.946)and 0.887 (0.835, 0.943), indicating the absence of significant differences in the parameters. During the treatment period, 9(45%) subjects reported 16 treatment emergent adverse events (TEAE), among which 6 subjects (30%) reported 9 TEAEs and 1 subject (5%) reported 1 TEAE during famitinib or omeprazole administered alone respectively, 5 subjects (25.0%) reported 6 TEAEs during in the combined administration phase. Omeprazole did not have a significant influence on the pharmacokinetics (PK) of famitinib and SHR116637, and the safety profile was good upon co-administration. ClinicalTrials.gov identifier NCT 05,041,920.

Keywords Gastric pH-dependent drug interactions · Omeprazole · Pharmacokinetics · Famitinib

Introduction

The oral administration route of tyrosine kinase inhibitors (TKIs) offers effectiveness in both solid and hematologic malignancies and is convenient for the patients, however, despite these advantages, it also causes a highly relevant new problem. Of recently approved orally administered cancer therapeutics, > 50% are characterized as having pH-dependent solubility [1–3]. The poor and variable pH-dependent solubility, together with other variable pharmacokinetic factors, contribute to a significant patient variability in plasma levels and exposure. Next to other factors, a majority of cancer patients frequently take acid–reducing agent (ARA) to alleviate gastroesophageal symptoms, thereby raising the potential for a gastric pH-dependent drug interaction [1]. This type of DDI may have detrimental effects on the efficacy of TKIs, with major clinical impacts described for some orally administrated targeted therapies (erlotinib, gefitinib, pazopanib, palbociclib), and conflicting results with many others, including nilotinib or dasatinib [1, 4, 5]. Long-term suppression of gastric acidity could decrease the absorption of certain major oral anticancer drugs with pH-dependent solubility and result in subsequent failure of therapy. To address this, guidelines are provided by the FDA and the European Medicines Agency (EMA) that recommend studying the DDI between pH-dependent drugs and ARAs.

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Famitinib (famitinib-malate, SHR1020, Fig. 1A) is a novel and potent multi-targeted receptor TKI that targets at c-kit, vascular endothelial growth factor receptor 2 and 3 (VEGFR-2 and 3), platelet-derived growth factor receptor (PD-GFR), FMS-like tyrosine kinase-3 receptor (FLT3) and protooncogene tyrosine kinase receptor (RET), as shown in Fig. 1 [6, 7]. Due to its anti-angiogenic effect, it was effective against metastatic renal cell carcinoma, non-small cell lung cancer and metastatic breast cancer [8–10]. Clinical trials of famitinib in combination with the concurrent medication or chemoradiotherapy also showed its good antitumor abilities against other solid tumors such as metastatic urothelial carcinoma, advanced immunomodulatory triple-negative breast cancer, advanced nasopharyngeal carcinoma and gastric cancer, etc. [6, 11–17]. A phase I study showed that famitinib had favorable PK characteristics and was generally well-tolerated. The major circulating metabolite SHR116637 was the formation of N-desethyl famitinib (Fig. 1B), which is pharmacodynamically active but exhibits a lower potency than the parent drug [18]. Within the dosing range of 4–27 mg, the increase in C_{max} and $AUC_{0-24\,h}$ for famitinib and SHR116637 were proportional to the increase in dose level. The plasma level of SHR116637 is approximately equivalent to 3.6% of that of the parent drug, and both famitinib and SHR116637 were slowly removed from circulation [6]. After administration for 28 days, the degrees of famitinib accumulation in vivo were significantly lower than sunitinib and the major side effects were noted in terms of neutrocytopenia, thrombocytopenia and diarrhea, with particularly less severe fatigue and thrombocytopenia [6]. These toxicities had no significant accumulation while treatment proceeded, however, the common adverse events (AEs) of gastrointestinal reactions, such as nausea and diarrhea, needed ARAs and gastric mucosal protective to alleviate these AEs.

According to the FDA guidance's decision tree on the evaluation of gastric pH-dependent drug interactions, DDI studies with ARAs are required if the drug dissolution is too low to determine the effect of pH on drug solubility or the solubility of the drug at pH 6.0–6.8 is less than dose divided by 250 mL [2]. Famitinib has been classified as a BCS class IV drug (low solubility, low permeability) by the FDA. The results of in vitro solubility test showed that the solubility of famitinib was 85, 140 and 8 μg/mL in the medium system of pH 1.0, 4.5, 6.8 respectively. The magnitude of solubility change with increasing pH occurs at a pH of 6.0–6.8. It fits the above criteria, so it is necessary to explore the effects of pH on the PK of famitinib. Among all therapeutic agents, PPIs are the most prevalent and most potent ARAs and with daily use produce a marked and sustained duration of acid suppression [1, 2]. A prospective study in four French Comprehensive Cancer Centers, more than a quarter of cancer patients used PPIs, mostly on a daily basis and in the long term [19]. As PPIs generally have a longer duration of suppression effect on gastric acid secretion than H_2 blockers and antacids do, they are expected to interfere with the intestinal absorption of TKIs to a greater extent [4]. In this paper, omeprazole, was therefore chosen for the study of famitinib with an PPI. We aim to update the potential gastric pH-dependent drug interactions between omeprazole and famitinib in healthy subjects, as well as to ascertain the safety of co-administration of famitinib and omeprazole.

Method

Study design

The screening was performed from day-7 to day-1. Eligible subjects were admitted to the Phase I clinical trial ward on day-1, provided a light diet in the evening, and then fasted for 10 h. On day 1, each subject was administered famitinib as a single oral 25 mg dose. Blood samples were collected before administration (within 1 h), 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 144 and 192 h after dosing. On day 10 through 22, subjects were orally daily administered 40 mg of omeprazole at least 0.5 h before breakfast, with the exception of day 15. On day 15, famitinib (25 mg) was administered concomitantly with omeprazole (40 mg), and the collection of the blood samples was the same as that on day 1. During the study period, all drugs were administered with approximately 240 mL water under a fasting condition, on day 1 and day 15, water was forbidden within 1 h before and after the study drug administration, and food was to be avoided within 4 h after administration. On day 23, all subjects were discharged after examination in the morning.

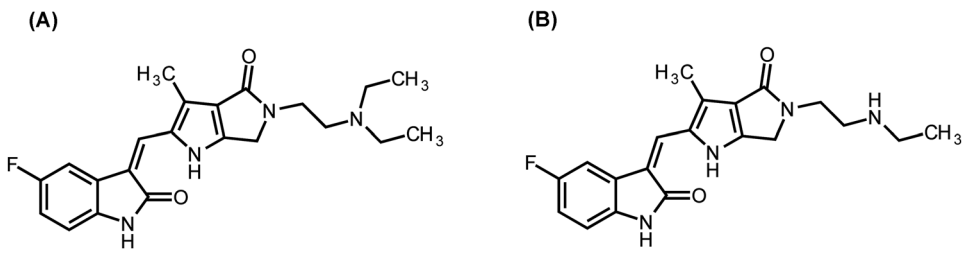

Fig. 1 Chemical structures of Famitinib **A** and the metabolite SHR116637 **B**

Subjects returned to the research center for follow-up or telephone follow-up from day 28 to day 30. A safety assessment was performed during the entire test period. A flowchart of this study is presented in Fig. 2.

Participants

Informed consent was signed before the trial, healthy male and female subjects aged between 18 and 45 (inclusive), of which no less than 1/3 are female subjects. The bodyweight of male subjects was ≥ 50 kg, and that of females was ≥ 45 kg; The body mass index should range between 19–28 kg/m^2. Creatinine clearance (CLCr) ≥ 80 mL/min. Key exclusion criteria included QTcF > 470 ms for women or > 450 ms for men, Any history of dysphagia or any gastrointestinal disease that affects drug absorption, uncontrolled peptic ulcer, colitis, pancreatitis, etc. Full eligibility criteria are included in the Supplementary Methods.

Formulations

Jiangsu Hengrui Pharmaceuticals produced and supplied famitinib capsules (specification: 25 mg/capsule, Lot: 200906NS). Omeprazole magnesium enteric-coated tablets (specification: 20 mg/tablet, Lot: SAMU) were also provided by Jiangsu Hengrui Pharmaceuticals.

PK assessment

The plasma concentration of famitinib and SHR116637 was determined by liquid chromatography-tandem mass spectrometry (LC–MS/MS). The analytical method was developed and validated to meet the standard operating procedure established by the sponsor. The concentration range of calibration standards for famitinib and SHR116637 was both 0.05–100 ng/mL. In each analytical batch, the number of quality control samples (QC) accounts for more than 5% of the total number of samples, and at least two samples at each concentration level per time. For famitinib, the inter-run precision was 2.9–4.1%, while the inter-run accuracy ranged between 1.3–3.1%. For the metabolite SHR116637, the inter-run precision and accuracy were 1.6–3.4% and -2.7–1.1%, respectively.

Safety assessment

Safety was monitored by measurements of vital signs (blood pressure, heart rate and temperature), physical examination clinical laboratory tests and 12-lead electrocardiogram. Tolerability was assessed by recording adverse events (AEs). Details of any AEs were recorded, including the AEs types, incidence, severity (graded according to NCI-CTCAE5.0), onset and end time, serious AEs, correlation with the test drug, and outcomes.

Pharmacokinetic and Statistical Analysis

The PK parameters of above analytes were calculated using a standard noncompartmental analysis method (NCA) by Phoenix WinNonlin (Pharsight Corporation 8.3 or higher). The main evaluation indices were C_{max} (maximum plasma concentration), the area under the curve of plasma concentration–time from zero to the last measurable concentration calculated by the linear trapezoid method (AUC_{0-t}), and the area under the curve of blood concentration from zero to infinity ($AUC_{0-\infty}$). The secondary evaluation indices were T_{max}, elimination halflife ($t_{1/2}$), apparent clearance rate (CL/F), and apparent volume of distribution (Vz/F). In addition, CL/F and Vz/F were not applicable to the metabolite SHR116637.

Statistical analysis was carried out using SAS v 9.4 (SAS Institute, Cary, NC, USA). Descriptive statistics and lists of PK parameters of the analyte were conducted and mean concentration–time curves were plotted. After natural log transformation, a mixed-effect model was used to fit PK parameters. Based on this model, the drugs were considered as fixed effects and the volunteers as random effects. The GMRs (co-administration of famitinib and omeprazole, and administration of famitinib alone) and their 90% CIs were estimated.

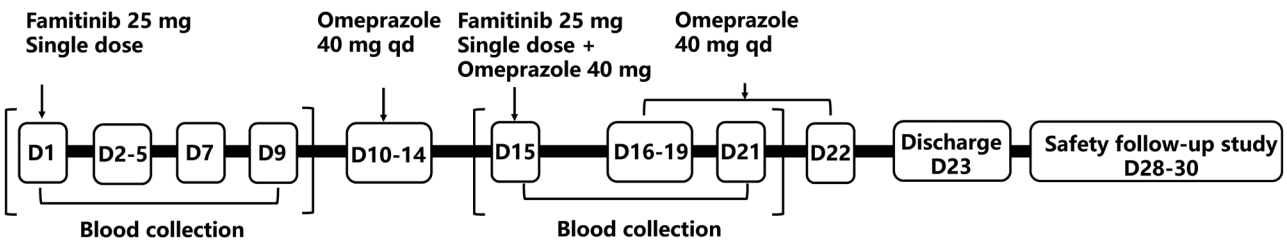

Fig. 2 The study design of the evaluation of gastric pH-dependent drug interactions between famitinib and omeprazole

Results

Subject demographics

Among the 20 Chinese subjects, there were 13 males and 7 females; 18 were of Han nationality and 2 were of other nationalities. The median age was 24.5 years (range 19–37 y), and the average height (± SD) was 168.38 ± 8.291 cm. The average body weight (± SD) was 69.09 ± 10.337 kg, and the average body mass index (± SD) was 24.26 ± 2.333 kg/m^2.

PK analysis

The main PK parameters of famitinib and its metabolite SHR116637 between famitinib alone and co-administration with omeprazole were showed in Tabel 1. No clinically significant difference was observed in the C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of famitinib between alone monotherapy and co-administration with omeprazole. The GMRs of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of famitinib were 98.9%, 95.6% and 95.3%, respectively. The exposure of the metabolite SHR116637 was slightly decreased when famitinib was co-administered with omeprazole, with the C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of SHR116637 decreased by 14.9%, 11.0% and 11.3% upon co-administration. The GMRs of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ for SHR116637 were 85.1%, 89.0% and 88.7%, respectively. Evaluation of drug interactions between famitinib and omeprazole was shown in Tables 1 and 2. The mean plasma concentration–time curve is shown as Fig. 3. The plasma concentrations of famitinib were similar over time, and there was no significant change in PK parameters between administration of famitinib alone and co-administration with omeprazole.

Safety analysis

All the 20 subjects enrolled in this study completed 2 times of famitinib and 13 times of omeprazole administration as planned. A total of 9 (45.0%) subjects had 16 AEs, all of which were treatment-emergent adverse events (TEAEs) at grade 1 severity. No adverse events of grade 2 or above were reported. Among the total 16 AEs, 9 TEAEs occurred in 6 subjects (30.0%) in the single administration phase of famitinib; 1 subject (5.0%) had 1 TEAE in the single administration of omeprazole; At the stage of famitinib combined with omeprazole, 5 subjects (25.0%) had 6 TEAEs. A summary of the above TEAEs was shown in Table 3. 5 (25.0%) subjects had 10 TEAEs related to famitinib including alanine aminotransferase increased (10%), blood triglycerides

Table 1 Summary of pharmacokinetic parameter analysis of famitinib and SHR116637

Administration mode	Pharmacokinetic parameters(unit)	Famitinib			SHR116637		
		Mean ± SD	Geometric Mean (CV%)	Median (minimum–maximum)	Mean ± SD	Geometric Mean (CV%)	Median (minimum–maximum)
Famitinib	T_{max}* (h)	5.65 ± 0.875	-	6.00 (3.00, 7.00)	5.8 ± 1.64	-	5.00 (5.00, 12.00)
	C_{max} (ng/mL)	43.2 ± 7.8	42.5 (19.6)	43.8 (25.7, 55.3)	1.9 ± 0.5	1.8 (28.9)	1.9 (1.2, 3.1)
	$AUC_{0\text{-}t}$ (h·ng/mL)	1425.5 ± 296.3	1395.0 (22.1)	1391.2 (778.0, 2052.3)	115.8 ± 44.6	108.2 (39.4)	108 (46.0, 201.4)
	$AUC_{0\text{-}\infty}$ (h·ng/mL)	1450.8 ± 312.0	1417.9 (22.7)	1407.1 (787.6, 2125.6)	128.0 ± 52.2	118.9 (41.0)	119.3 (50.8, 233.6)
	$t_{1/2}$ (h)	32.5 ± 5.6	32.1 (17.0)	31.3 (24.6, 45.5)	53.2 ± 9.4	52.4 (17.3)	51.7 (40.0, 76.3)
	CL/F (L/h)	18.1 ± 4.4	17.6 (22.7)	17.8 (11.8, 31.7)	-	-	-
	Vz/F (L)	837.7 ± 221.2	815.3 (23.3)	794.9 (529.6, 1606.4)	-	-	-
Famitinib + Omeprazole	T_{max}* (h)	6.7 ± 1.03		6.50 (5.00, 8.00)	6.9 ± 2.07		6.50 (5.0, 12.0)
	C_{max} (ng/mL)	42.7 ± 7.3	42.0 (18.2)	42.4 (28.0, 57.6)	1.6 ± 0.5	1.5 (33.5)	1.5 (0.9, 2.8)
	$AUC_{0\text{-}t}$ (h·ng/mL)	1355.0 ± 247.1	1333.2 (18.8)	1312.7 (885.1, 1875.5)	101.7 ± 34.6	96.3 (35.4)	97.1 (53.9, 185.4)
	$AUC_{0\text{-}\infty}$ (h·ng/mL)	1375.1 ± 257.0	1351.9 (19.3)	1321.8 (895.1, 1915.0)	111.7 ± 38.8	105.5 (36.1)	106.9 (58.1, 203.3)
	$t_{1/2}$ (h)	32.0 ± 4.7	31.7 (14.0)	30.7 (26.3, 44.5)	52.8 ± 9.2	52.2 (16.3)	51.6 (40.1, 81.5)
	CL/F (L/h)	18.8 ± 3.7	18.5 (19.3)	18.9 (13.1, 27.9)	-	-	-
	Vz/F (L)	859.7 ± 161.7	846.0 (18.4)	825.6 (618.8, 1272.6)	-	-	-

*:T_{max} expressed in median (minimum, maximum), the other parameters were expressed as Mean ± SD and Geometric Mean(CV%)

Table 2 Statistical analysis of pharmacokinetic parameters of famitinib and SHR116637

Agent	Pharmacokinetic parameters(unit)	Geometric Mean		Ratios (90% CI)	CV (%)
		Famitinib + Omeprazole	Famitinib		
Famitinib	C_{max} (ng/mL)	42.0	42.5	0.989(0.953, 1.027)	6.8
	$AUC_{0\text{-}t}$ (h·ng/mL)	1333.2	1395.0	0.956(0.907, 1.007)	9.5
	$AUC_{0\text{-}\infty}$ (h·ng/mL)	1351.9	1417.9	0.953(0.905, 1.005)	9.6
SHR116637	C_{max} (ng/mL)	1.5	1.9	0.851(0.786, 0.920)	14.5
	$AUC_{0\text{-}t}$ (h·ng/mL)	96.3	108.2	0.890(0.838, 0.946)	11.1
	$AUC_{0\text{-}\infty}$ (h·ng/mL)	105.5	118.9	0.887(0.835, 0.943)	11.2

increased (10%), gamma-glutamyl transferase increased (5%), basophil count increased (5%), white blood cells urine positive (5%), glucose urine present (5%), and blood glucose increased (5%). 2 (10.0%) subjects had 2 TEAEs related to omeprazole including gamma-glutamyl transferase increased (5%) and increased heart rate. All adverse events occurred during the study period were recovered / resolved at the end of the study.

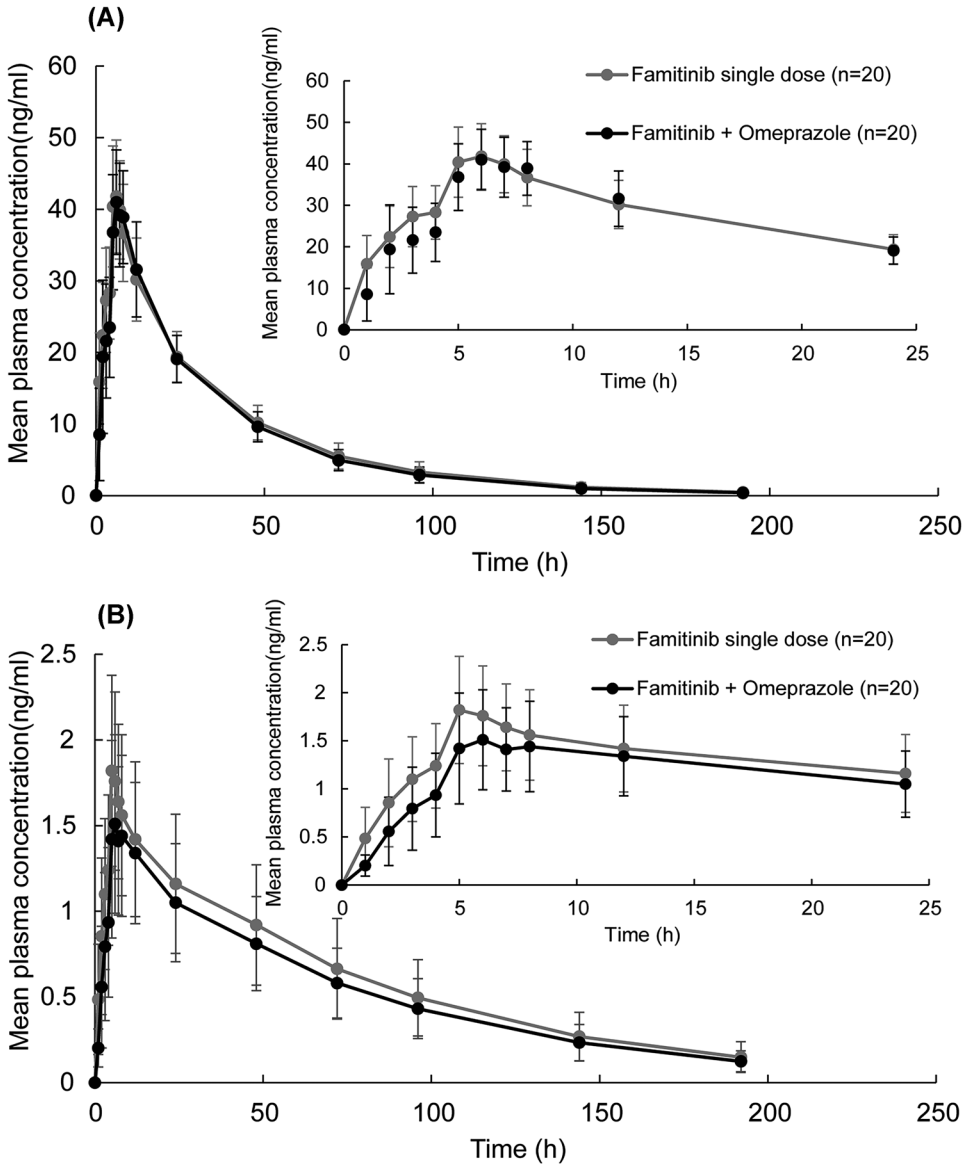

Fig. 3 The mean plasma concentration versus time profile for famitinib **A** and SHR116637 **B** after oral administration of famitinib 25 mg with and without omeprazole

Table 3 Summary of treatment emergent adverse events

Adverse event	Famitinib		Omeprazole		Famitinib + Omeprazole		Total	
	N = 20		N = 20		N = 20		N = 20	
	n(%)	Incidence	n(%)	Incidence	n(%)	Incidence	n(%)	Incidence
Any treatment-emergent adverse event	6 (30.0%)	9	1 (5.0%)	1	5 (25.0%)	6	9 (45.0%)	16
Gamma-glutamyl transferase increased	0	0	0	0	1 (5.0%)	1	1 (5.0%)	1
Alanine aminotransferase increased	2 (10.0%)	2	0	0	0	0	2 (10.0%)	2
White blood cells urine positive	1 (5.0%)	1	0	0	0	0	1 (5.0%)	1
Glucose urine present	1 (5.0%)	1	0	0	0	0	1 (5.0%)	1
Basophil Count increased	1 (5.0%)	1	0	0	1 (5.0%)	1	1 (5.0%)	2
Heart rate increased	1 (5.0%)	1	0	0	1 (5.0%)	1	2 (10.0%)	2
Blood triglycerides increased	2 (10.0%)	2	0	0	0	0	2 (10.0%)	2
Blood glucose increased	1 (5.0%)	1	0	0	0	0	1 (5.0%)	1
Blood pressure decreased	0	0	1 (5.0%)	1	2 (10.0%)	3	2 (10.0%)	4

Disscusion

Early assessment of pH-dependent DDIs for TKIs of poorly soluble and weakly acidic compounds offers various advantages for patient safety. Retrospective data suggest that TKI plasma concentration is decreased in patients receiving concomitant PPIs or H_2 antagonists therapy with subsequently poorer oncologic outcomes, such as crizotinib, dasatinib, erlotinib, gefitinib, lapatinib and pazopanib, and recommended avoiding concomitant use of [20]. However, another recent systematic review and meta-analysis of the use of gastric-acid suppressants and oral anticancer treatments supported the evidence of a possible negative impact of such combinations [21]. To our knowledge, this is the first study to assess the PK and safety effects of omeprazole on the potent TKIs famitinib as well as its major metabolite SHR116637 in healthy subjects. Our findings suggested that omeprazole did not significantly impact the PK properties of both famitinib and SHR116637, demonstrating good safety on co-administration.

Key factors in the design of a pH-dependent DDI study include study population, selection of ARAs, type of crossover design (randomized or single-sequence), and the dose/dosing regimen etc. [2]. Previous clinical trials have demonstrated that famitinib showed linear dose-related pharmacokinetic characteristics in the dosing range of 4–27 mg. The recommended dose for phase II clinical trials is 25 mg. Hence, for the safety evaluation, the dose of famitinib was selected to be 25 mg. The main PK parameters were similar in terms of C_{max}, AUC and $t_{1/2}$ between the patients with advanced solid cancer and healthy subjects. Food intake was unlikely to impact on the PK of famitinib [6]. As a result, the study conducted under the fasted condition as it was likely to represent the worst-case scenario and can help guide cancer patients' treatment. For the selection of ARAs, omeprazole was chosen for 1) PPIs generally have a longer duration of suppression effect on gastric acid secretion than H_2 blockers and antacids do, and are expected to interfere with the intestinal absorption of WBDs to a greater extent and a worst-case scenario in the in vivo evaluation of the pH effect. 2) Famitinib was mainly metabolized by CYP3A4/5 and CYP1A1/2, Furthermore, famitinib is a weak inhibitor of CYP3A4, but it's unlikely to affect CYP3A4 due to a single dose at 25 mg (0.22 μM) in this study. As one of the most commonly used PPIs in clinic, omeprazole gives its high affinity for CYP2C19 and moderate affinity for CYP3A4, However, no obvious effect was detected in the present study, and it was widely used in the gastric pH-dependent drug interaction of TKIs such as erlotinib and sorafenib which were also metabolized by CYP3A4 [4, 22]. In addition, a self-control study was also used to overcome the influence of enzyme differences between individuals. The common dose of omeprazole is 20 mg qd, which can achieve maximum suppression of gastric acid within ~ 4 days, and the expected effect of a 40-mg dose follows a similar time course [20]. Therefore, a second dose of famitinib was administered after 5 days omeprazole administration to ensure that subjects achieved maximum inhibition of gastric-acid secretion.

Compared with famitinib single-dose administration, the geometric mean of $AUC_{0-\infty}$ was slightly reduced when famitinib was co-administered with omeprazole (1417.927 vs. 1351.939 h·ng/mL, decreased by approximately 4.7%), along with the C_{max}, T_{max}, $t_{1/2}$, CL/F and Vz/F did not significantly differ between the two phases. The least squares GMRs of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (90% CIs) of famitinib combined with omeprazole to famitinib alone were 0.989 (0.953, 1.027), 0.956 (0.907, 1.007) and 0.953 (0.905, 1.005) respectively, indicating the absence of significant differences in AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of famitinib when compared with famitinib alone. The metabolite SHR116637 data was consistent

with the reduced absorption famitinib, and the metabolic ratio remained similarly small for both treatment arms with 0.075 versus 0.081 for famitinib and famitinib plus omeprazole, respectively. The median T_{max} of famitinib metabolite SHR116637 was 5.00 h and 6.50 h, indicating that the peak time of famitinib metabolite SHR116637 was slightly prolonged after omeprazole combined with famitinib. The C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ decreased by 14.9%, 11.0% and 11.3% for famitinib and famitinib plus omeprazole, respectively. The least squares GMRs of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ (90% CIs) of SHR116637 between coadministration group and alone group were 0.851 (0.786, 0.920), 0.890 (0.838, 0.946)and 0.887 (0.835, 0.943) respectively. Except the lower limit for the SHR116637 GMR of C_{max} (90% CIs) is 78.6%, the least squares GMRs of $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max} (90% CIs) of both famitinib and SHR116637 are all in the range of 80%-125%. Compared the "no concomitant PPIs" versus "concomitant PPIs" based on their clinical characteristics, the exposure of metabolite SHR116637 is approximately equivalent to 9.47% and 8.72% of that of the parent drug, so it has little effect on the PK of famitinib.

According to one completed phase-I clinical trial, the most common AEs of famitinib included neutrocytopenia, thrombocytopenia and diarrhea. In some cases, it can also result in elevation of blood lipids and glucose [6, 18]. In our study, we also assessed the safety profile of combination therapy in the present study, compared with the above AEs, most AEs observed in the present study was mild, such as increased gamma-glutamyl transferase, increased basophil count, increased heart rate, alanine aminotransferase, blood glucose increased, blood triglycerides elevated, the positive urine test for leukocyte-esterase and sugar. During the treatment period, a total of 6 (30.0%) subjects had 9 AEs during famitinib alone, and 1 (5.0%) subject had 1 AE during the mutiple dose of omeprazole, while 5 (25.0%) subjects had 6 AEs during famitinib combined with omeprazole. Less severe and less frequent side effects were noted after the co-administration of omeprazole and famitinib compared with the single phase of famitinib, revealing the safety and tolerability of famitinib and omeprazole coadministration in clinical settings. Co-administration of famitinib and omeprazole was associated with good safety.

Conclusions

To conclude, the effect of PPIs on the efficacy of certain anticancer agents, particularly TKIs, is a major issue in daily practice. In this opinion paper, although the famitinib has pH-dependent solubility in vitro, the PPI omeprazole had minimal effect on the PK of famitinib and SHR116637 in healthy subjects. Therefore, famitinib as a formulated tablet can be administered with or without PPIs, such as omeprazole. In addition, interactions caused by other factors involved in absorption, apart from the pH effect, need to be considered during drug development on a case-by-case basis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10637-022-01299-3.

Acknowledgements This work was supported by Jiangsu Hengrui Co. Ltd. The authors thank all the patients who participated in this study and their families, as well as all the investigators and site staff who made the study possible.

Author Contributions Linlin Hu and Huiping Wang contributed to the study conception and design. Material preparation, data collection and analysis were performed by Linlin Hu, Mingmin Cai, Wei Qian, Lu Tang, Qiuyue Sun and Ting Dou. The first draft of the manuscript was written by Linlin Hu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This project was also supported by the National Natural Science Foundation of China (No. 81503340), and the National Natural Science Foundation of Jiangsu Province (No. BK20150645), and the Project of scientific research plan for drug supervision, Grant/Award Number: 202106. We thank staff involved.

Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Competing interests The authors declare no competing interests.

Informed consent Informed consent was obtained from all individual participants included in the study.

Research involving human participants and/or animals This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was approved (approval number, 2021ZDSYLL195-P01) by the Ethics Committee of the Zhongda Hospital, Medical School, Southeast University (Nanjing, China).

Conflict of interest statement The authors declare no conflicts of interest. The author reports no conflicts of interest in this work.

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